Journal of the American College of Cardiology
© 2002 by the American College of Cardiology Foundation
Published by Elsevier Science Inc.

Vol. 39, No. 8, 2002
ISSN 0735-1097/02/$22.00
PII S0735-1097(02)01751-5

Left Ventricular Assist Device Therapy Improves Utilization of Donor Hearts

Keith D. Aaronson, MD, MS,* Michael J. Eppinger, MD,† David B. Dyke, MD,* Susan Wright, BS, RN,† Francis D. Pagani, MD, PHD, FACC†

Ann Arbor, Michigan

OBJECTIVES We sought to determine the survival experiences of patients bridged to heart transplantation with either intravenous (IV) inotropes or an implantable left ventricular assist device (LVAD).

BACKGROUND Because of the operative risks of LVAD implantation and the reported lower mortality associated with inotropic therapy, bridging to heart transplantation with inotropes is thought to be the preferred treatment option.

METHODS Between April 1, 1996, and May 10, 2001, a total of 104 patients were bridged to heart transplantation with either IV inotropes (n = 38) or an implantable LVAD (n = 66; HeartMate). Survival was compared (Kaplan-Meier method) for three periods: survival to transplantation, post-transplantation survival and overall survival (i.e., survival from the onset of bridging to follow-up).

RESULTS Survival to transplantation was 81 ± 5% at three months for the LVAD group and 64 ± 11% for the inotrope group (p = NS). Post-transplantation survival was 95 ± 4% at three years for the LVAD group (two deaths) and 65 ± 10% at three years for the inotrope group (nine deaths; p = 0.007). Overall survival was 77 ± 6% at three years for the LVAD group and 44 ± 9% at three years for the inotrope group (p = 0.01).

CONCLUSIONS Overall survival for patients who were bridged to heart transplantation with an implantable LVAD was superior to that of patients who were bridged with inotropes. Bridging to transplantation with an implantable LVAD improves utilization of donor hearts. (J Am Coll Cardiol 2002;39:1247–54) © 2002 by the American College of Cardiology Foundation

Both intravenous (IV) inotropes and a left ventricular assist device (LVAD) can be used to bridge patients successfully to heart transplantation when standard oral medications are inadequate. In standard contemporary practice, IV inotropes are initially preferred because of the substantial risk of early mortality and morbidity associated with LVAD use (1–3). In contrast, inotropic therapy is associated with low morbidity and mortality (4).

However, consideration of the different mortality risks associated with inotropic and LVAD therapy during the bridging and post-transplantation periods suggests the possibility that LVAD therapy may be the preferred initial bridging strategy. Although the risk of dying while receiving

See page 1255

IV inotropes is lower than the risk with LVAD therapy in the first few weeks, this advantage might diminish with longer United Network for Organ Sharing (UNOS) status 1 waiting times (5). End-organ function may remain impaired during inotropic therapy, and patients often remain bedbound. However, LVAD bridging allows relatively superior recovery of end-organ function and more significant rehabilitation, with the potential for better post-transplantation outcomes (6–8).

We retrospectively reviewed the pre- and post-transplantation outcomes of patients bridged to transplantation with either LVAD or IV inotropic therapy. We hypothesized that overall survival, including both the pre- and post-transplantation periods, would be superior in the LVAD group, and that fewer deaths would occur in the LVAD group in the post-transplantation period. This outcome would be expected to improve donor heart utilization.

METHODS

We retrospectively evaluated the survival experience of adult patients (age ≥17 years) who were treated with IV inotropes or an implantable LVAD as a bridge to transplantation at the University of Michigan Medical Center from April 1, 1996 (our acquisition date for the HeartMate LVAD [Thoratec, Inc., Pleasanton, California]) to May 10, 2001, with follow-up through May 10, 2001. During this period, 66 patients were bridged with either a HeartMate Implantable Pneumatic or Vented Electric LVAD (LVAD group). The inotrope group consisted of 38 patients who were bridged exclusively with one or more IV inotropes administered continuously in the hospital (n = 34) or at home (n = 4), with UNOS 1, 1A or 1B waiting-list status. Patients who began therapy with an IV inotrope but later

From the *Division of Cardiology and †Section of Cardiac Surgery, University of Michigan, Ann Arbor, Michigan.

Manuscript received July 26, 2001; revised manuscript received November 5, 2001, accepted January 30, 2002.

Abbreviations and Acronyms

ECMO = extracorporeal membrane oxygenation
IV = intravenous
LVAD = left ventricular assist device
UNOS = United Network for Organ Sharing
VAD = ventricular assist device
VSD = ventricular septal defect

required LVAD therapy were considered only in the LVAD group; the onset of bridging support for these patients was taken as the time of LVAD implantation. Only patients receiving an implantable LVAD were considered in the analysis of the LVAD group.

We evaluated survival for three periods: 1) survival to transplantation (survival from the onset of bridging support [initiation of IV inotropes and UNOS status 1, 1A or 1B status for the inotrope group; LVAD implantation for the LVAD group] to heart transplantation); 2) post-transplantation survival (survival from transplantation to the end of follow-up); and 3) overall survival (survival from the onset of bridging support to the end of follow-up). Actuarial survival was calculated by the Kaplan-Meier method. For survival to transplantation, the survival time was censored at the time of transplantation.

Follow-up was complete for all patients. For comparative purposes, we also examined the post-transplantation survival experiences of patients who underwent UNOS status 2 transplantation during the same period.

The study protocol was approved by the Institutional Review Board for Human Investigation at the University of Michigan (October 25, 2001).

Statistical analysis. Data are presented as the mean value ± SD or median value. Survival time comparisons between groups were made using the log-rank test (SPSS version 10.1; SPSS Inc., Chicago, Illinois). The number of deaths occurring after transplantation in the LVAD and inotrope groups was compared using the two-tailed Fisher exact test. A comparison of mean values was performed by using analysis of variance and the independent sample *t* test with the Bonferroni correction for multiple comparisons. Statistical significance was defined at $p < 0.05$.

RESULTS

There were no significant differences in age, gender or etiology of heart failure between the groups (Table 1). The cardiac index at the initiation of bridging was significantly ($p < 0.05$) greater in the inotrope group than in the LVAD group (Table 1). There were no significant differences between the groups in heart rate, mean arterial pressure, mean pulmonary artery pressure, pulmonary capillary wedge pressure, right atrial pressure or pulmonary vascular resistance.

At the time of LVAD implantation, 15 patients (23%) were supported with extracorporeal membrane oxygenation (ECMO) or an extracorporeal ventricular assist device (VAD); 20 (30%) were supported with two or more inotropes, with or without a vasopressor; 12 (18%) were supported with a single inotrope; 14 (21%) were supported with intra-aortic balloon counterpulsation, with or without additional inotropic support; and 5 (8%) received antiarrhythmic agents only, without inotropic support for severe life-threatening ventricular arrhythmias.

Table 1. Patient Characteristics at Initiation of Bridging to Transplantation

	LVAD Group (n = 66)	Inotrope Group (n = 38)
Age (yrs)	49 ± 13	49 ± 15
Gender		
Male	51 (77%)	27 (71%)
Female	15 (23%)	11 (29%)
Etiology		
Ischemic	39 (59%)	17 (45%)
Nonischemic	27 (41%)	21 (55%)
Hemodynamic data		
Heart rate (beats/min)	88 ± 20	90 ± 19
MAP (mm Hg)	73 ± 12	76 ± 8
RAP (mm Hg)	12 ± 6	13 ± 7
MPAP (mm Hg)	32 ± 9	34 ± 9
PCWP (mm Hg)	23 ± 7	24 ± 7
CI (l/min per m^2)	2.0 ± 0.6*	2.6 ± 0.9
PVR (Wood's unit)	2.4 ± 1.4	2.3 ± 1.0

*Significantly ($p < 0.05$) different from the inotrope group. Data are presented as the mean value ± SD or number (%) of patients.
CI = cardiac index; LVAD = left ventricular assist device; MAP = mean arterial pressure; MPAP = mean pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; RAP = right arterial pressure.

In the inotrope group, 10 patients (26%) were listed as UNOS status 1A, 14 (37%) as UNOS status 1B and 14 (37%) as UNOS status 1 (previous UNOS listing criteria). Nineteen patients (50%) were supported with high-dose IV inotropic therapy, defined as: 1) dopamine or dobutamine ≥7.5 μg/kg per min; 2) milrinone ≥0.5 μg/kg per min; 3) multiple inotropes with dopamine or dobutamine ≥5 μg/kg per min and milrinone >0.25 μg/kg per min; or 4) any dose of an inotrope in combination with norepinephrine or neosynephrine. Nineteen patients (50%) were supported with low-dose IV inotropic therapy (not meeting the criteria for high-dose inotropic therapy). Five patients in the inotrope group were placed on ECMO (n = 2) or received an intra-aortic balloon pump (n = 3) for acute hemodynamic deterioration or ventricular arrhythmia 24 to 48 h before death or transplantation. These five patients did not receive LVAD therapy, because of technical issues (post-infarct ventricular septal defect [VSD], n = 1; mechanical aortic prosthesis and previous mediastinitis with sternal wound closure by a rectus muscle transposition flap, n = 1) or the development of complications contraindicating transplantation immediately after the initiation of ECMO or intra-aortic balloon pump support (n = 3).

Of the 38 patients in the inotrope group, 22 (58%) were potential candidates for LVAD therapy, if necessary, but the attending cardiologist determined they were clinically stable

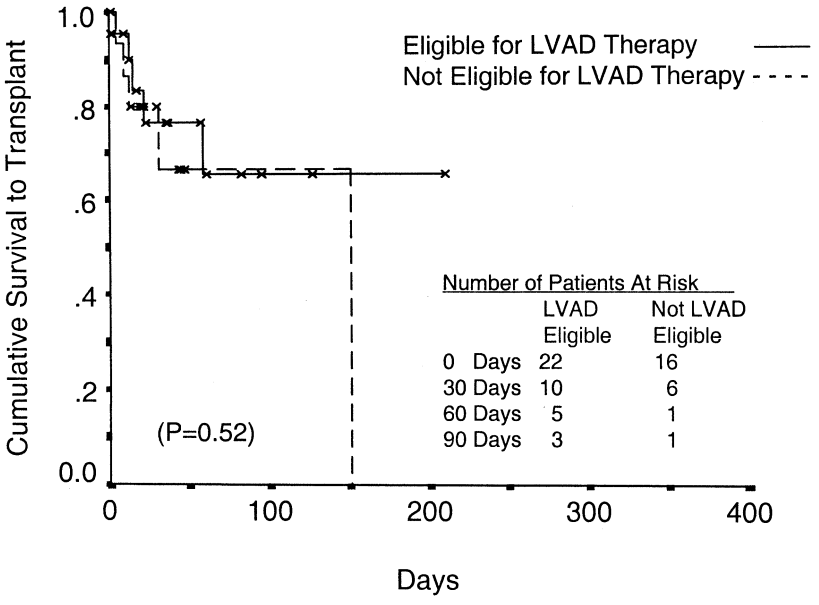

Figure 1. Survival to transplantation of patients in the inotrope group who were potentially eligible for left ventricular assist device (LVAD) therapy and those ineligible because of high-risk factors.

on inotropic therapy. Sixteen patients (42%) in the inotrope group were thought to have characteristics making them either very high risk or ineligible for LVAD therapy, such as a small body surface area (n = 7), complex congenital heart disease (n = 5), hypertrophic cardiomyopathy (n = 1), ascending aortic aneurysm (n = 1), post-infarct VSD (n = 1) and mechanical aortic prosthesis and previous mediastinitis with sternal wound closure by a rectus muscle transposition flap (n = 1). Survival to transplantation was not significantly different (p = 0.52) different between patients in the inotrope group who were potentially eligible for LVAD therapy and those ineligible because of high-risk factors (Fig. 1).

Survival to transplantation. Of the 66 patients in the LVAD group, 48 (73%) survived to transplantation, 12 (18%) died before transplantation and 6 (9%) are still on the waiting list. Of the 38 patients in the inotrope group, 28 (74%) survived to transplantation and 10 (26%) died before transplantation (Table 2). Actuarial survival on the waiting list for the two groups is shown in Figure 2. For the LVAD group, survival to transplantation was 81 ± 5% at one and three months (and all the way to 11.5 months), with a median time to transplantation of 2.9 months; all pre-transplantation deaths occurred by 19 days after LVAD implantation (Table 2). Survival to transplantation without LVAD therapy for the inotrope group was 78 ± 8% at one month and 64 ± 11% at three months, with a median time to transplantation of 2.9 months. Although waiting-list survival appears to deteriorate with longer waiting times for the inotrope group, the survival curves were not significantly different (p = 0.2).

Post-transplantation survival. Forty-eight patients in the LVAD group and 28 patients in the inotrope group received a heart transplant. The characteristics for these patients and for 60 patients who received an UNOS status-2 transplant during the same period are shown in Table 3. There were no significant differences between patients in the LVAD group and those in the inotrope group in terms of the recipient's

Table 2. Causes of Death Before and After Transplantation

	LVAD Group (n)	Inotrope Group (n)
Pre-transplantation causes of death	Cerebrovascular accident (1) Device failure (1) Hemorrhage (1) Multisystem organ failure/sepsis (5) Right-sided circulatory failure (4) (n = 12)	Cerebrovascular accident (1) Multisystem organ failure/sepsis (4) Sudden death (2) Refractory cardiogenic shock (3) (n = 10)
Post-transplantation causes of death	Cerebrovascular accident (1) Rejection (acute) (1) (n = 2)	Cerebrovascular accident (1) Infection (3) Hemorrhage (1) Primary allograft dysfunction (1) Rejection (acute) (3) (n = 9)

LVAD = left ventricular assist device.

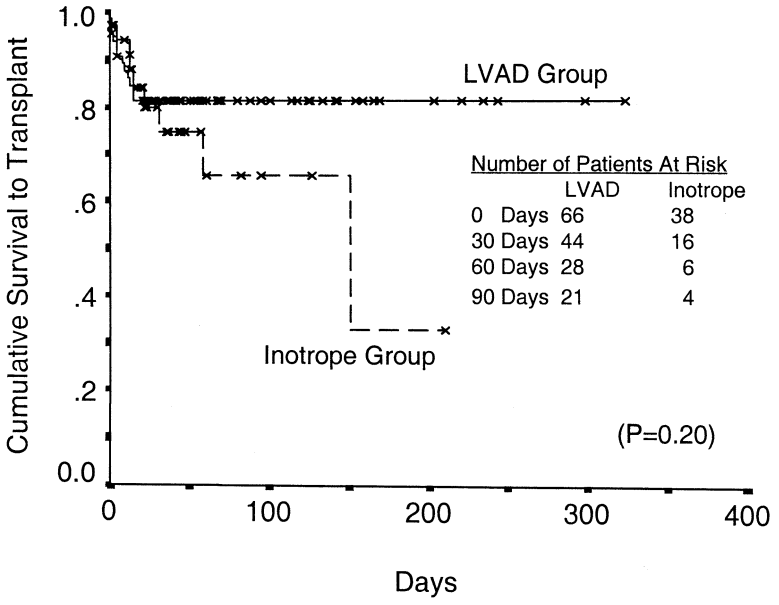

Figure 2. Survival to transplantation: left ventricular assist device (LVAD) group versus inotrope group.

age, the donor's age, gender, the donor and recipient's weight and height, etiology of heart failure, allograft ischemic time or pre-transplantation length of stay. Serum creatinine and total bilirubin were significantly ($p < 0.05$) lower in the LVAD group than in the inotrope group at the time of transplantation (0.99 ± 0.34 mg/dl vs. 1.48 ± 0.59 mg/dl and 0.75 ± 0.39 mg/dl vs. 0.98 ± 0.47 mg/dl, respectively). Fewer post-transplantation deaths occurred in the LVAD group than in the inotrope group (2 [4%] of 48 patients in the LVAD group vs. 9 [32%] of 28 patients in the inotrope group; $p = 0.045$), despite a similar duration of follow-up and pattern of censoring (Table 2). Post-transplantation actuarial survival rates for the LVAD and inotrope groups are shown in Figure 3. Post-transplantation survival was significantly better for the LVAD group (98 ± 2% at one year and 95 ± 4% at three and four years) than for the inotrope group (74 ± 9% at one year and 65 ± 10% at three and four years; $p = 0.007$). Improved post-transplantation survival with LVAD therapy resulted in a much lower death rate in the first year, after which the survival experiences for both groups were similar.

To investigate the hypothesis that patients in the inotrope group who were not eligible for LVAD therapy because of technical reasons were more ill, which would have adversely affected post-transplantation survival in this group, we analyzed post-transplantation survival in the inotrope group according to whether patients were considered as potential candidates (n = 22) or not

Table 3. Patient and Donor Characteristics at Heart Transplantation

	LVAD Group (n = 48)	Inotrope Group (n = 28)	UNOS Status 2 Group (n = 60)
Recipient age at transplantation (yrs)	46 ± 13*	49 ± 15	52 ± 13
Donor age (yrs)	33 ± 13	28 ± 12*	37 ± 14
Gender			
Male	35 (73%)	19 (68%)	39 (65%)
Female	13 (27%)	9 (32%)	21 (35%)
Etiology			
Ischemic	24 (50%)	11 (39%)	36 (60%)
Nonischemic	24 (50%)	17 (61%)	24 (40%)
Recipient weight (kg)	77 ± 13	74 ± 17	77 ± 17
Donor weight (kg)	79 ± 16	83 ± 16	77 ± 16
Recipient height (cm)	172 ± 10	172 ± 8	170 ± 10
Donor height (cm)	172 ± 10	177 ± 8*	170 ± 10
Total LOS (days)	59 ± 57*	55 ± 60*	23 ± 22
Post-transplant LOS (days)	20 ± 16	16 ± 9	17 ± 11
Allograft ischemic time (min)	184 ± 38	184 ± 44	188 ± 41
Waiting time to transplantation (months)	4.6 ± 5.1* [2.9]	7.2 ± 7.9 [2.9]	10.3 ± 7.6 [9.6]

*Significantly ($p < 0.05$) different from the UNOS status 2 group. Data are presented as the mean value ± SD, number (%) of patients or [median value].

LOS = length of stay in hospital; LVAD = left ventricular assist device; UNOS = United Network for Organ Sharing.

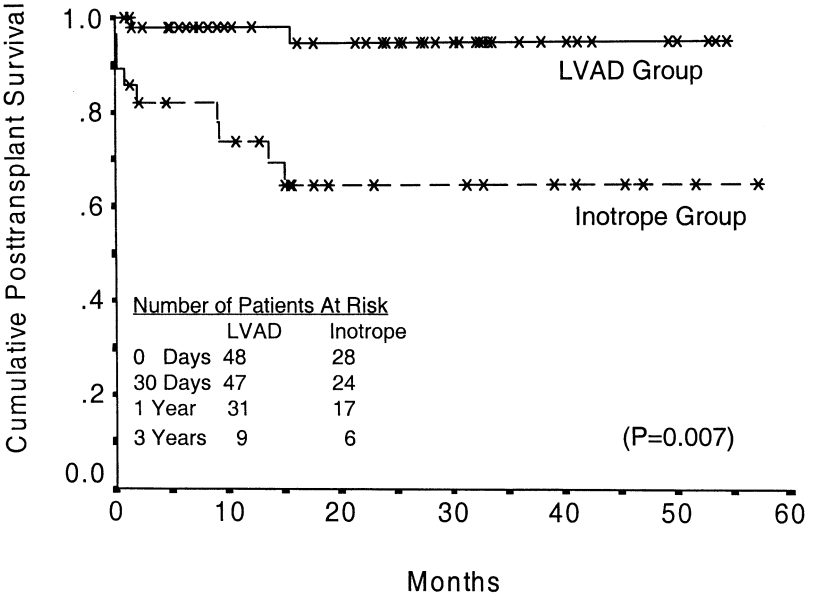

Figure 3. Post-transplantation survival: left ventricular assist device (LVAD) group versus inotrope group.

eligible (n = 16) for LVAD therapy. Patients not eligible for LVAD therapy because of technical reasons had superior, but not significant, post-transplantation survival, as compared with patients considered as potential candidates for LVAD therapy (Fig. 4).

Post-transplantation survival for patients who received an UNOS status-2 transplant was 86 ± 4%, 77 ± 7% and 77 ± 7% at one, three and four years, respectively. There was a nonsignificant trend (p = 0.1) toward improved survival for patients in the LVAD group, as compared with those patients awaiting an UNOS status-2 transplant, as shown in Figure 5. The recipient age of patients in the LVAD group was significantly younger than that of patients awaiting an UNOS status-2 transplant (Table 3). The donor age of patients awaiting an UNOS status-2 transplant was significantly older that that of the inotrope group, but was not different from that of the LVAD group. The waiting time to transplantation of UNOS status-2 patients was significantly longer than that of patients who received a transplant while on LVAD support.

Overall survival. Overall survival for the LVAD and inotrope groups from the onset of bridging support is shown in Figure 6. Actuarial survival was significantly better for the LVAD group (80 ± 5% at one year and 77 ± 6% at three

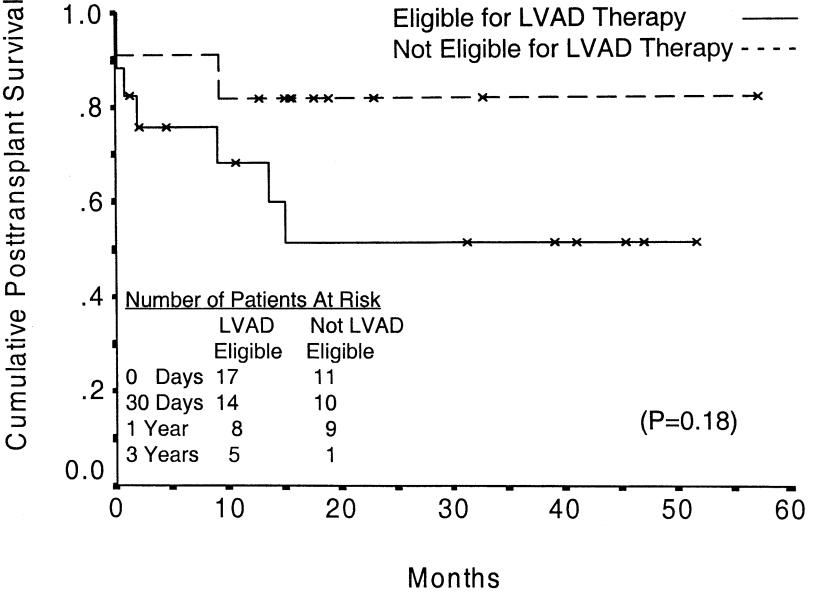

Figure 4. Post-transplantation survival: inotrope group only (classified into patients who were potential candidates for left ventricular assist device [LVAD] therapy and those considered not eligible because of high-risk factors).

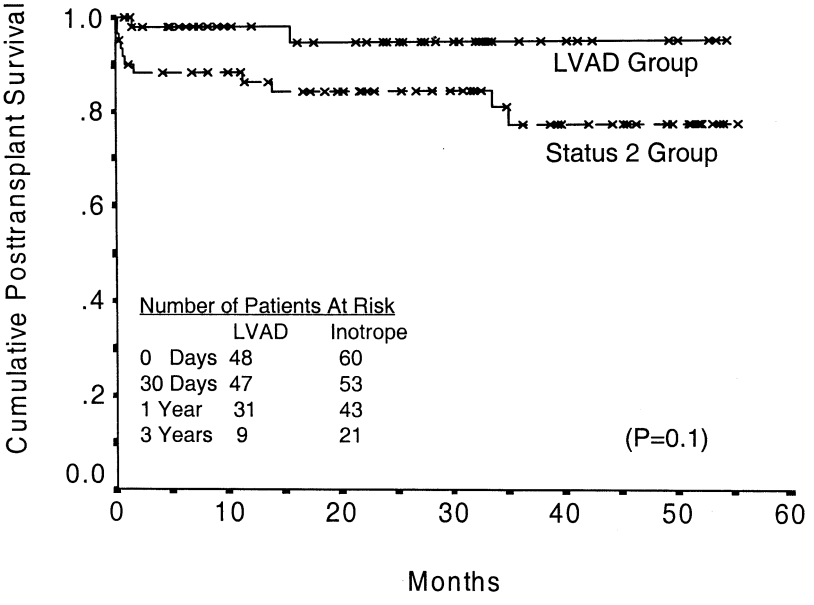

Figure 5. Post-transplantation survival: left ventricular assist device (LVAD) group vs. patients transplanted as United Network for Organ Sharing status 2.

and four years) than for the inotrope group (56 ± 8% at one year and 44 ± 9% at three and four years; p = 0.03 vs. LVAD group).

DISCUSSION

Overall survival for patients who were bridged to transplantation with an implantable LVAD was superior to that of patients who were bridged with IV inotropes. This resulted from a nonsignificant trend toward improved survival up to transplantation and a statistically significant improvement in post-transplantation survival (i.e., donor heart survival) for the LVAD group. These data demonstrate that the early perioperative mortality associated with LVAD implantation is offset by improved survival with longer waiting times to transplantation and improved post-transplantation survival. Given the critical shortage of donor organs, a substantial benefit of LVAD bridging is the improved utilization of donor hearts.

Frazier et al. (6) reported on the outcomes of 19 patients bridged to heart transplantation with the pneumatic HeartMate LVAD. When these patients were compared with 12 historic control subjects who met the criteria for enrollment in their trial, but did not receive the device, survival to transplantation was significantly improved in those receiving mechanical circulatory support. Survival to transplantation at 60 days was 100% in the device group and ~20% in

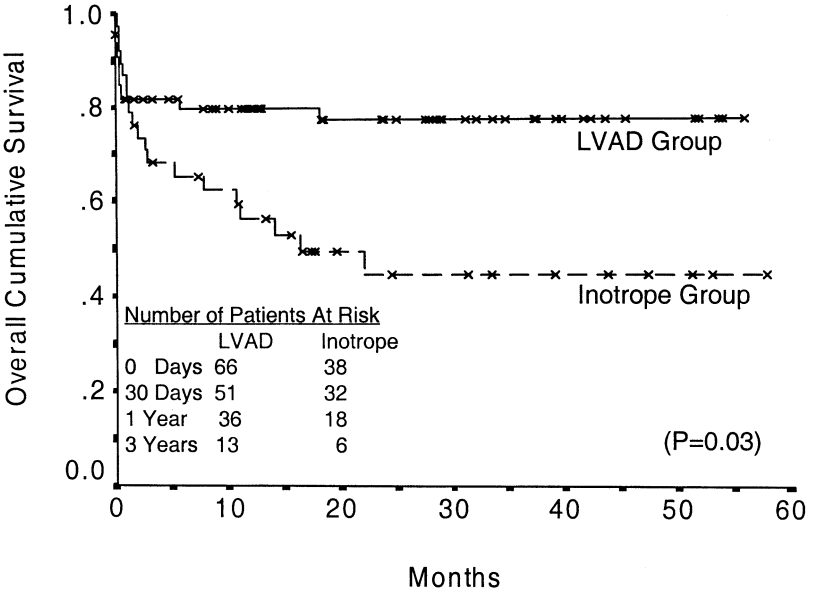

Figure 6. Overall survival from the time of bridging to follow-up: left ventricular assist device (LVAD) group versus inotrope group.

control subjects. In a follow-up multicenter study including 75 patients who had a device implant and 33 control subjects, 71% of those with a device survived to transplantation, as compared with 36% of control subjects (7). The one-year post-transplantation survival rate was 90% in patients with mechanical circulatory support and 67% in control subjects. Massad et al. (8) compared transplantation outcomes in 53 patients receiving mechanical circulatory support as a bridge to transplantation with the HeartMate LVAD with 203 patients who were transplanted without LVAD support (both UNOS status 1 and 2). Neither, post-transplantation length of stay, operative mortality nor one-year transplantation survival (94% for the LVAD group and 88% for the group without mechanical support) was significantly different between the groups. Bank et al. (9) also assessed transplantation outcomes in 26 patients who, while awaiting transplantation on inotropic therapy, deteriorated clinically, requiring consideration for LVAD therapy. Twenty patients received an LVAD and six remained on inotropic therapy. After transplantation, the incidence of renal failure and right heart failure was significantly higher in the group of patients remaining on inotropic therapy. Six-month survival was not significantly different between the groups.

More recently, Jaski et al. (10) from the Cardiac Transplant Research Database Research Group reported on the heart transplant outcomes of patients supported with LVAD versus IV inotropic therapy. The survival of 502 patients receiving LVAD support was not significantly different from the 2,514 patients receiving inotropic therapy as a bridge to transplantation. Multivariate Cox regression analysis did not identify LVAD as a significant risk factor for mortality. The LVAD recipients had a significantly lower rate of freedom from first infection, as compared with the inotrope group. Freedom from rejection was not different between the groups. The differences in the conclusions reached in our study and those by Jaski et al. (10) may be attributed to the inclusion of extracorporeal VADs and the earlier period of LVAD implants (i.e., before 1996). Further, differences in the acuity of illness (i.e., degree of inotropic support [high-dose vs. low-dose]) between patients on IV inotropes at the time of transplantation may have existed.

The registry of the International Society of Heart and Lung Transplantation has identified the VAD as an independent risk factor for post-transplantation mortality (11). However, this registry includes both extracorporeal, paracorporeal and implantable LVADs, as well as patients with biventricular or univentricular support, and the data were accumulated over an extended period. Thus, it is difficult to extrapolate these findings to our study, which included a more homogeneous group with only implantable LVADs during a more recent period. The reasons for our observation that LVAD therapy improves overall survival may reflect an improved knowledge base of selection criteria for optimal LVAD candidates (3), as well as a willingness to allow full recovery of end-organ function and rehabilitation before considering transplantation. Only 4 (8.3%) of 48 patients received a heart transplant within 30 days of LVAD implantation, and serum creatinine and total bilirubin were significantly lower in the LVAD group than in the inotrope group at the time of transplantation.

Observations from the present study and previous reports support the conclusion that patients requiring prolonged inotropic therapy have a poor survival rate while they wait for a heart transplant. In a retrospective review of prognostic indexes of 125 heart transplant candidates being admitted for inotropic therapy, Gronda et al. (5) reported a one-year survival rate of 65% for patients requiring inotropic support as a bridge to heart transplantation. In patients who required IV pharmacologic circulatory support for more than 21 days and did not receive a suitable donor heart within this period, >50% of patients died while waiting for a heart transplant. These authors suggested implantation of a circulatory assist device in this high-risk group awaiting heart transplantation for longer than 21 days. These data, in conjunction with data that support survival with LVAD bridging to transplantation approaching 75% to 80% (8), suggest that LVAD therapy may be the therapy of choice in patients requiring prolonged inotropic therapy.

Study limitations. There are a number of limitations of this study. First, this was a retrospective review, and conclusions were based on a small, nonrandomized sample of patients. However, a number of factors suggest that patients in the LVAD group were more severely ill than those in the inotrope group. Patients in the inotrope group had a significantly higher cardiac index at the time of bridging. Also, 50% of patients receiving inotropic therapy had stable hemodynamic data on low-dose inotropes, whereas nearly half of the patients treated with an LVAD required either ECMO, an extracorporeal VAD or an intra-aortic balloon pump at the time of LVAD bridging. Furthermore, donor age, which is a significant determinant of transplantation survival (11), was significantly younger for patients transplanted in the inotrope group. Despite these important biases in favor of inotrope therapy, post-transplantation survival for patients in the LVAD group was significantly better than that in the inotrope group.

Conclusions. Treatment with LVAD as a bridge to heart transplantation appears to yield significantly improved overall long-term survival and, importantly, conserves donor hearts. With longer waiting times to transplantation and improving trends in LVAD survival, LVAD therapy, as opposed to prolonged inotropic therapy, may be the preferred method of bridging to heart transplantation.

Reprint requests and correspondence: Dr. Francis D. Pagani, Section of Cardiac Surgery, 2120 Taubman Center, Box 0348, 1500 East Medical Center Drive, Ann Arbor, Michigan 48109. E-mail: fpagani@umich.edu.

REFERENCES

1. McCarthy PM, Smedira NO, Vargo RL, et al. One hundred patients with the HeartMate left ventricular assist device: evolving concepts and technology. J Thorac Cardiovasc Surg 1998;115:904–12.
2. McCarthy PM, Schmitt SK, Vargo RL, Gordon S, Keys TF, Hobbs RE. Implantable LVAD infections: implications for permanent use of the device. Ann Thorac Surg 1996;61:359–65.
3. Oz MC, Goldstein DJ, Pepini P, et al. Screening scale predicts patients successfully receiving long-term implantable left ventricular assist devices. Circulation 1995;92 Suppl II:II169–73.
4. Canver CC, Chanda J. Milrinone for long-term pharmacologic support of the status 1 heart transplant candidates. Ann Thorac Surg 2000;69:1823–6.
5. Gronda EG, Barbieri P, Frigerio M, et al. Prognostic indices in heart transplant candidates after the first hospitalization triggered by the need for intravenous pharmacologic circulatory support. J Heart Lung Transplant 1999;18:654–63.
6. Frazier OH, Macris MP, Myers TJ, et al. Improved survival after extended bridge to cardiac transplantation. Ann Thorac Surg 1994; 57:1416–22.
7. Frazier OH, Rose EA, McCarthy P, et al. Improved mortality and rehabilitation of transplant candidates treated with a long-term implantable left ventricular assist system. Ann Surg 1995;222:327–36.
8. Massad MG, McCarthy PM, Smedira NG, et al. Does successful bridging with the implantable left ventricular assist device affect cardiac transplantation outcome? J Thorac Cardiovasc Surg 1996;112:1275–83.
9. Bank AJ, Mir SH, Nguyen DQ, et al. Effects of left ventricular assist devices on outcomes in patients undergoing heart transplantation. Ann Thorac Surg 2000;69:1369–75.
10. Jaski BE, Kim JC, Naftel DC, et al. Cardiac transplant outcome of patients supported on left ventricular assist device versus intravenous inotropic therapy. J Heart Lung Transplant 2001;20:449–56.
11. Hosenpud JD, Bennett LE, Keck BM, Fiol B, Boucek MM, Novick RJ. The Registry of the International Society for Heart and Lung Transplantation: Sixteenth Official Report 1999. J Heart Lung Transplant 1999;18:611–26.